Pollution, Politics, and Vultures

Andrew Balmford

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whereas the mass spectrometry screen of Di Virgilio *et al*. reveals additional proteins that interact with phosphorylated 53BP1, raising the possibility that some of them might join Rif1 in shielding DNA ends.

53BP1 has stood out as a molecular shield against 5′ DNA-end resection at double-strand breaks without a clear mechanism attached to it. Adding Rif1 to the picture breaks this deadlock and provides the much-needed impetus to mechanistically explore DNA-end protection by addressing previously unforeseen questions. The recent studies by Escribano-Díaz *et al*. (*2*) and Ross Chapman *et al*. (*3*) provide an important lead by showing that during G_1 phase of the cell division cycle, Rif1 opposes the function of the complex involved in DNA-end resection, composed of BRCA1 and C-terminal binding protein-interacting protein (CtIP) (*1*). Conversely, after entry into S phase and activation of cyclin-dependent kinases, the phosphorylated BRCA1-CtIP complex prevails, unloads Rif1 from chromatin, and initiates DNA-end resection. This neatly explains how periodicity of the cell cycle is linked to repair pathway choice, but additional mechanisms should not be discounted. For instance, Rif1 is a multifunctional protein that organizes higher-order chromatin structure at origins of DNA replication. It is possible that chromatin accessibility contributes to restraining DNA resection at double-strand breaks (*8*, *9*).

Other unresolved issues include how Rif1 binds to phosphorylated 53BP1 and how the activated BRCA1-CtIP complex disrupts this interaction. The absence of a phospho-recognition motif in the Rif1 sequence indicates that enhanced interaction between 53BP1 and Rif1 after DNA damage is mediated by a hitherto unknown molecular linker. This is not merely an academic problem—mechanisms that influence DNA-end resection have a therapeutic potential in cancer (*10*), and if we are to expand the list of targets for more efficient synthetic treatments with modalities that involve DNA breakage (radiotherapy, many forms of chemotherapy), factors that enhance recognition of phosphorylated 53BP1 by Rif1 after DNA damage could be of crucial relevance as targets for therapeutic interventions. Regardless, defining the role of Rif1 in human diseases associated with unstable genomes deserves attention, and the discovery of its function in DNA-end processing is an important milestone toward achieving this goal.

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ECOLOGY

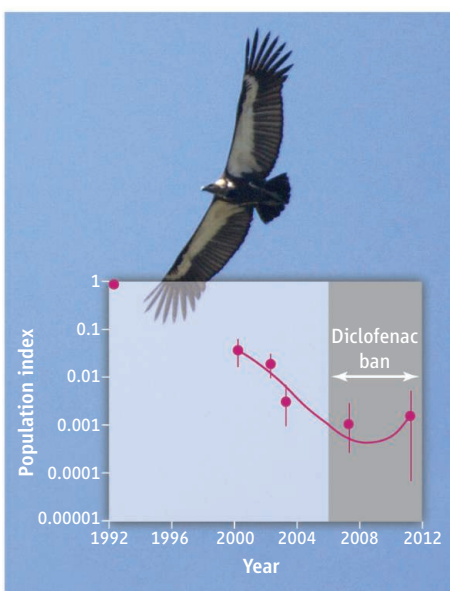
Pollution, Politics, and Vultures

The catastrophic collapse of south Asia's vultures may at last be coming to an end, thanks to a ban on the veterinary drug responsible.

Andrew Balmford

Fifty years after the publication of Rachel Carson's groundbreaking book *Silent Spring*, environmental pollutants, whose impacts are hard to diagnose and harder still to control, continue to cause grave damage to nontarget organisms. The range of substances of concern has expanded since Carson's day from nutrients, pesticides, and heavy metals and now includes pharmaceuticals. Although drug pollution problems have been particularly difficult to address (*1*), recent developments in south Asia offer some positive news on one of the best-known examples. Scientists and politicians are at last making progress in reversing the accidental but catastrophic poisoning of the region's vultures by a widespread veterinary drug.

Two decades ago, vulture populations across the Indian subcontinent began a collapse to just 1% of what they had been (*2*). As well as being a crisis for bird conservation, this was a serious problem for public health, because it ended the free disposal by the birds of the region's vast annual tonnage of cattle carcasses (*3*). Ten years after the decline began, its cause was finally identified: The vultures were being poisoned by widespread use of the out-of-patent nonsteroidal anti-inflammatory drug diclofenac, which causes kidney failure when the birds feed on carcasses of recently treated cattle (*4*).



Turning a corner? Changes in population indices of the oriental white-backed vulture *Gyps bengalensis*, from 6 years of repeat surveys of a large number of road transects in India. Vertical lines show 95% confidence limits derived by bootstrapping; the curve shows the cubic log-linear trend for 2000 to 2011. The *y* axis has a logarithmic scale.

Based on evidence that deaths of vultures by diclofenac were widespread and frequent and that contamination of cattle carcasses was sufficient to account for the rapid decline (*5*), the governments of India, Pakistan, and Nepal banned the veterinary use of diclofenac in 2006. Bangladesh followed suit in 2010, and in May 2012 the four governments reached an unprecedented political agreement to further coordinate and improve actions to prevent adverse effects of veterinary drugs on vultures (*6*).

These responses were a considerable achievement for conservation science, but the diclofenac ban did not solve the vulture problem overnight. Surveillance of diclofenac contamination of cow carcasses in India soon after the ban showed little change (*7*), and test purchases in pharmacies found

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diclofenac formulated for human use widely on sale for the treatment of cattle (*8*). These findings, coupled with coordinated efforts by nongovernmental organizations (NGOs) and governments, led to further restrictions and remedial efforts. By 2008, diclofenac contamination had fallen substantially (*7*), largely as a result of two factors: awareness-raising work by NGOs and government departments with the public, pharmaceutical industry, and veterinarians; and the identification and promotion of the alternative drug meloxicam, which is effective for treating cattle but does not harm vultures (*9*).

A suite of studies of the latest vulture population trends suggests that these efforts are working and that the vulture declines have slowed or even stopped. In India, all three critically endangered *Gyps* vultures did not decline between 2007 and 2011; one species, the oriental white-backed vulture, may have increased slightly (*10*). Population models indicate that these changes match predictions from the measured reduction in carcass contamination (*7*, *10*). The oriental white-backed vulture population in Nepal has also increased since the ban, and the decline of this species in Bangladesh has slowed since the more recent ban there. A long-billed vulture population in Pakistan, which was declining before the ban in 2006, has now increased substantially (*11*).

It seems that carefully targeted research—combined with political commitment and government-NGO cooperation—is making a real difference for the subcontinent's vultures. Yet, recovery will likely be partial and take decades. Continued monitoring of vultures and of veterinary drugs and their toxicity is necessary to measure the effectiveness of interventions and suggest modifications where necessary.

This need for vigilance and adaptive management is underscored by the increased use of several other veterinary drugs with unknown effects on vultures: aceclofenac, a precursor of diclofenac that is highly likely to be toxic (*12*), and ketoprofen, which was shown to be toxic to vultures 3 years ago (*13*) but is still permitted for veterinary use in India. The governments of the vulture range states have moved much faster and more effectively than did western governments when responding to the environmental impacts of organochlorine pesticides identified by Rachel Carson, but sustained scientific scrutiny is vital, as is continued political resolve.

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APPLIED PHYSICS

Metamaterials with Quantum Gain

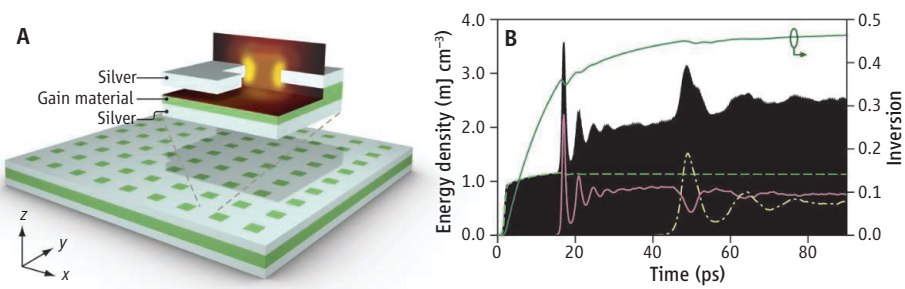
Integrating amplifying media with metamaterials allows loss-free plasmonic operation and opens a route for controlling nanoscale quantum emitters.

Ortwin Hess and Kosmas L. Tsakmakidis

Optical metamaterials and nanoplasmonics offer extreme control and localization of light within volumes that can be smaller than a cubic light wavelength by more than three orders of magnitude, but they suffer from appreciable dissipative losses. This weakness is thought to constitute the prime impediment before many of the envisaged applications can succeed in practice. However, recent breakthroughs in the theoretical understanding and experimental fabrication of gain-enhanced metamaterials and nanoplasmonic heterostructures promise to overcome these hindrances, while allowing for new ways to control spontaneous and stimulated emission of light on the nanoscale (*1*, *2*).

Resistive losses in nanoplasmonic metamaterials arise from the interaction of the incident photons with the quasi-free conduction electrons of the metals, thereby constituting an inherent feature of the response of metal-based nanodevices. For truly subwavelength plasmonic structures, these losses follow universal laws; that is, they do not depend on the particular geometric configuration but only on the metal used (usually noble metals) (*3*). Meanwhile, there has been an increased emphasis on two-dimensional (2D) metasurfaces, which are much more convenient to fabricate than their full-3D metamaterial counterparts but can steer light in equally dramatic ways, well below the fundamental diffraction limit and over broad, flat areas (*4*).

In such a 2D nanostructure with laser dyes (gain medium) incorporated into its fabric (see the figure, panel A), the objective is to obtain optimum coupling of the plasmonic excitations to the gain molecules, so that maximum harnessing of the gain medium can be achieved—a requirement due to the high losses. When the pattern of the nanoholes periodically perforating the two silver nanofilms is engineered such that the desired plasmonic resonance coincides with



Playing for gain. (**A**) An illustration of the gain-enhanced optical metamaterial, with a magnified unit cell and an example of plasmonic field enhancement at two vertical planes inside the cell. (**B**) Energy and average inversion (green solid line, right axis) inside the lasing nanofishnet over time. The signals, time-averaged over 0.4 ps (black), are decomposed into the pump mode (green dashed line), the bright mode (red solid line), and the dark mode (yellow dash-dotted line).

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